

Increased Use of Medical Services and Antibiotics by Children Who Claim a Prior Penicillin Sensitivity

MICHAEL J. KRAEMER, MD; HOPE CAPRYE-BOOS, MS, ARNP, and HENRY S. BERMAN, MD, *Spokane, Washington*

On surveying 3,467 children (ages 0 to 19 years) who were members of a health maintenance organization in Spokane, Washington, we found that 95 of 1,497 respondents (6.3%) claimed a past intolerance to penicillin-like agents. We investigated the costs of providing medical care for these 95 children and a random sample of 187 children who did not claim prior penicillin sensitivity. During a two-year period of observation, the children who claimed prior penicillin reactions had a significant increase in the average number of medical visits, the average number of antibiotic prescriptions, the average wholesale cost of antibiotic prescriptions and the average antibiotic cost per patient per month of observation. These children have an increased exposure to antibiotics that may increase their risk for adverse drug reactions.

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Penicillin hypersensitivity reactions are common. They usually appear as a drug-induced exanthem but can occasionally be an explosive, life-threatening systemic reaction. Penicillins remain the most common cause of drug-induced anaphylaxis,^{1,2} resulting in several hundred drug-related deaths each year.³

Penicillin hypersensitivity from oral or parenteral exposures to these drugs may develop in children as well as in adults. The actual prevalence in the pediatric age group is unclear although estimates range from 5% to 20%. Only a minority of the patients who claim a penicillin hypersensitivity actually have a true allergic sensitivity. In a recent clinical skin-testing trial, only 8.75% of children who claimed some prior reaction had positive skin tests (which implies a current allergic potential), and in only an additional 1% of those who did not react to skin tests did an exanthem develop with a ten-day course of penicillin.⁴ In many children a transient rash or gastrointestinal reaction can appear either from the infection itself or from a toxic reaction to the antibiotic. If improperly interpreted as an allergic reaction, the child would be labeled as "penicillin-allergic." He or she would then be encouraged to use alternative antibiotics like sulfonamides, erythromycins, tetracyclines or cephalosporins.

This research was undertaken to study the subset of children who claim a prior sensitivity to penicillin without regard to the validity of their claims. We wished to define any discriminating characteristics for the children who claim this sensitivity and to assess the impact of this claim on the cost of their medical care.

Patients and Methods

Allergy Questionnaire

We designed a questionnaire to assess the prevalence of common childhood allergic disorders: chronic dermatitis, allergic rhinitis, asthma, food hypersensitivities, stinging insect reactions and penicillin sensitivity. This was mailed to the parents of 3,467 children (ages 0 to 19 years), approximately 50% of the membership of a health maintenance organization, Group Health of Spokane (Washington). The questionnaire included a form containing the necessary elements of informed consent as approved by Group Health of Spokane that was signed by the parent or guardian of the child.

Of the 3,467 children sampled, 1,497 completed questionnaires were returned (43.2%). Parents who answered "yes" to "Has your child ever had a reaction to penicillin-like antibiotics?" were placed in the "claims penicillin sensitivity" category (N = 95). For comparisons, we selected a random sample of 187 children whose parents answered "no" to this question.

Medical Records Review

We reviewed the medical records for the two years preceding the time of the survey, noting any documentation of drug allergy claims in the drug allergy decal on the front of the chart, the patient data base and the ongoing progress notes. We recorded the total number of medical visits and antibiotic prescriptions during this two-year interval. The cost of each antibiotic prescription was determined by multiplying the prescription size by the wholesale drug cost

From the Spokane Allergy and Asthma Clinic (Dr Kraemer), the Intercollegiate Center for Nursing Education (Ms Caprye-Boos) and the Group Health of Spokane, Spokane, Washington (Dr Berman).

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during that year. The average monthly antibiotic cost for each child was determined by dividing the total drug costs by the total number of months of membership during that two-year observation period. For children who joined the health plan during the two-year interval and for children who reacted to penicillins during this interval, we used information only from the remaining months in the two-year interval of observation.

Statistical Analysis

Age and sex, claims of other allergic conditions, number of medical visits, number of antibiotic prescriptions obtained and the cost of antibiotics were compared for patients and controls. The mean and range of these variables are listed in the results. The absolute number and percentage are listed for proportions. For statistical analyses we used the Student's *t* test for age, the Wilcoxon signed ranks test for variables that were not normally distributed and the χ^2 test for proportions. A two-tailed probability was assumed when determining significance levels.

Results

A total of 1,497 persons returned the survey (43.2%). Of these, 95 children claimed a prior penicillin hypersensitivity (6.3%). Penicillin was the drug most often implicated for causing this reaction, although reactions were also claimed for ampicillin, amoxicillin and bacampicillin hydrochloride. In most instances (87%) the reaction occurred

after oral ingestion of the drug. With the design of our study, we could not determine if the rate of sensitization was greater with the oral or the parenteral route. Most of the reactions occurred in younger children (from birth to 3 years of age). The median time from the onset of treatment to the appearance of the reaction was one day, the range was up to nine days. The most common reactions were a pruritic red rash (53%), a nonpruritic fine papular red rash (38%) and large blotchy hives or angioedema (14%). Only four children recounted symptoms consistent with anaphylaxis. The median interval from the time of the reaction to the time of the survey was four years (range 0.1 to 18.6 years). The median age at the time of the reactions was 2.2 years (range 0.2 to 16.5 years). In this survey, 28 children who had their adverse penicillin reaction during the two-year observation period (incident cases) at the time of reaction ranged in age from 0.9 to 16.2 years (median age 1.8 years). None of these patients were admitted to hospital during this two-year interval. A physician confirmed that the rash was allergic in nature in 62 of the children. In none of the 95 cases was more than one suspected penicillin reaction reported. None had specific allergy skin testing to confirm their suspected penicillin hypersensitivity.

Of the 95 who claimed prior reactions on our survey, only 59% (56) had any documentation of their claim in the medical record. This could include a drug-allergy-alert sticker on the front of the chart (47% [45]), an adverse drug reaction claim in the patient data-base section of the med-

TABLE 1.—Clinical Characteristics of Patients and Controls

Clinical Characteristics	Patients, N=95	Controls, N=186	P Value
Age			
Mean, years	8.93	8.91	NS
Range, years	0.8 to 19.5	0.4 to 19.5	...
Sex			
Male, No. (%)	51 (54)	90 (49)	NS
Female, No. (%)	44 (46)	96 (51)	...
Allergic diagnoses			
Chronic pruritic dermatitis, No. (%)	17 (18)	17 (9)	<.05
Allergic rhinitis, No. (%)	20 (21)	18 (10)	<.01
Asthma, No. (%)	17 (18)	8 (4)	<.001
Food hypersensitivity, No. (%)	11 (12)	12 (6)	NS
Insect sting allergy, No. (%)	4 (4)	9 (5)	NS
Total physician visits in the 24-month observation period			
Mean, No. visits	5.49	3.27	<.001
Range, No. visits	0 to 39	0 to 19	...
Months of observation during the 24-month period			
0.0 to 5.9, No. (%)	11 (12)	17 (9)	
6.0 to 11.9, No. (%)	15 (16)	34 (18)	
12.0 to 17.9, No. (%)	14 (15)	19 (10)	
18.0 to 24.0, No. (%)	55 (58)	116 (62)	
Total antibiotic prescriptions in the 24-month period			
Mean	1.73	0.80	<.001
Range	0 to 14	0 to 9	...
Average antibiotic prescription costs per patient during 24-month period			
Mean, \$	4.60	1.75	<.001
Range, \$	0.00 to 59.92	0.00 to 21.99	...
Average antibiotic prescription costs per patient per month of observation			
Mean, \$	0.36	0.12	<.001
Range, \$	0.00 to 7.27	0.00 to 4.31	...

NS=no significance

ical record (26% [25]) or a specific notation of a drug allergic reaction in the patient progress notes (22% [21]).

Of the 187 control patients, only one patient who had no prior history of drug hypersensitivity on our survey had claimed an intolerance to penicillin-like agents on the patient data-base section of the chart (making a survey false-negative rate of 0.5%). This patient was excluded from the analysis.

Both patients and controls had similar ages (see Table 1). There was no significant sex difference. A history of chronic dermatitis, allergic rhinitis and asthma was significantly more common in the patient group. A history of food hypersensitivity and of stinging insect reactions was not different. There was a significant difference in the average number of medical visits during the two-year period of observation: 5.49 for patients and 3.27 for controls (Table 1). There was no difference in the number of months of observation between the two groups. A significant difference occurred in the average number of antibiotic prescriptions: 1.73 versus 0.80. There was also a significant difference in the average total cost per person of antibiotic prescriptions issued during the two years—\$4.60 versus \$1.75—and in the average antibiotic costs per month of observation—\$0.36 versus \$0.12. The range of these cost categories was broad, so nonparametric tests were used to determine the significance of the differences. In both groups, the number of antibiotic prescriptions written was maximal in the children younger than 4 years (135 prescriptions for 69 children).

During the two-year period of observation, 104 courses of non-penicillin antibiotics were issued to the children who claimed a past penicillin sensitivity, and 31 courses of penicillins were given to the same group. None of these patients who received the penicillin had documentation of any alleged penicillin sensitivity in their chart. Only one of these antibiotic courses resulted in a rash and subsequent withdrawal of the drug. There were no other adverse outcomes or allergic-like sensitivities noted with any of the penicillin-alternative antibiotics administered to these children.

Discussion

Several risk factors have been associated with the claim of a prior penicillin reaction. Young children and middle-aged adults are at an increased risk of a penicillin allergy developing.⁵ The median age of initial penicillin reaction for our group was younger than 2 years. It is likely that the increased incidence of penicillin reactions in this younger group is at least partly explained by this age group's increased exposure to antibiotics. The association of claiming a penicillin reaction with other allergic disease is controversial. Asthma and hay fever have not been more common in persons who actually react on skin tests to penicillins.^{6,7} Nonetheless, many earlier series have suggested a higher rate of claiming penicillin allergy in persons with other allergic disorders.^{8,9} It would seem that the likelihood of persons to claim a prior drug sensitivity is directly related to the likelihood of their being exposed and thus to being sensitized to that drug. It is possible that allergic patients are more likely to claim this sensitivity because of an increased exposure to penicillins to treat infectious dermatitis, purulent otitis and sinusitis. An alternative explanation is that this subgroup of allergic patients represents persons in whom cutaneous or gastrointestinal symptoms

develop more easily due to any number of nonallergic exposures, like infections, fevers or toxic reactions to drugs. We could not discern if a "diagnostic bias" also led parents of allergic children to more readily assert that their child's otherwise mild exanthem or reaction was a "drug allergy." Without specific skin testing we could not further evaluate these possibilities.

Several clinics have carefully evaluated patients who claim a past penicillin hypersensitivity. Using skin tests with major and minor penicillin antigens, they have shown that from 9% to 19% will actually show evidence of allergic sensitivity.^{5,10-12} Therefore, we assume that most of the children in our study are claiming an allergic sensitivity to the penicillins unnecessarily. While the history of their reaction is somewhat helpful, without confirmation by skin tests it is difficult to identify the truly allergic patients.

We have shown that the children who claim a prior penicillin hypersensitivity are more likely to seek medical care and to receive antibiotics. Their antibiotic costs were increased nearly threefold over the control group. They probably represent a sicker subset of children who more frequently require antibiotics for acquired infections. It has not been shown that these excess antibiotic costs could be decreased by more clearly evaluating their claim of penicillin allergy. A recent report by VanArsdel and co-workers suggests that routine penicillin skin testing could be safely and effectively used to determine if patients with a history suggesting penicillin allergy are no longer allergic, if they ever were.¹³ Before recommending routine penicillin skin testing for this group, we would suggest more careful study of the potential costs and benefits of this approach.

It is disconcerting that only 59% of those claiming a penicillin hypersensitivity in our questionnaire had it confirmed in their medical records. We compared this finding with a review of coronary care unit charts for adequacy of drug allergy documentation. In that study, only 40% of the charts had documentation of the allergy history.¹⁴ As in our survey, this failure to document drug allergy status occurred even though the information was usually available. The failure to document a drug allergy usually results from one of three causes: failure of a patient to confirm the sensitivity when casually questioned, failure of a physician or pharmacist to ask about previous drug reactions and failure to document the information in a conspicuous area of the chart. We feel that we had a higher proportion of positive histories with the allergy questionnaire because we used several questions to prompt information about prior allergic reactions.

We were also concerned that some patients who claimed a sensitivity in our survey had received penicillins during the two-year interval of observation. Not surprisingly, none of these patients had confirmation of a prior penicillin sensitivity in their charts. Fortunately, no serious adverse reactions occurred, most likely reflecting the very low prevalence of true penicillin allergy in this group. Nevertheless, as long as drug allergy documentation is inadequate, the potential exists for a serious reaction.

When prescribing antibiotics, physicians, nurses and pharmacists should routinely ask patients if they have previously received the drug and whether they had specific adverse effects. If they claim an adverse reaction, the drug should be avoided and a suitable alternative used. To prevent future penicillin reactions, it is essential to clearly

document any claims of prior sensitivities in a visible, conspicuous area of the medical chart.

At this time, patients who claim penicillin hypersensitivity should receive skin testing only if clinical judgment dictates that the alternative antibiotics would be ineffective or potentially more toxic. The major determinant skin test antigens are available as benzyl penicilloyl-polylysine (Pre-Pen; Kremers-Urban Company), but the minor determinant mixture awaits further testing before licensure.¹⁵ Until it is available, fresh penicillin G should be used. The skin testing confers a slight risk of an allergic reaction, so should be done only in a setting where appropriate emergency precautions are present. It should be interpreted by a person skilled in evaluating prick and intradermal skin tests. If penicillin skin tests are positive and there is still no alternative agent available, the patient should be cautiously desensitized to the penicillins. Several protocols have been used for desensitization.^{11,16-18} If the skin tests are negative, a low-dose penicillin should be given orally. If tolerated, the full therapeutic dose may then be given.

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